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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/081,309	02/21/2002	Michael Brandt	20859	3846

151 7590 07/26/2006

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PATENT LAW DEPARTMENT
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EXAMINER	
CHANDRA, GYAN	
ART UNIT	**PAPER NUMBER**
1646	

DATE MAILED: 07/26/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/081,309	BRANDT ET AL.	
	Examiner	Art Unit	
	Gyan Chandra	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 May 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-15* is/are pending in the application.

4a) Of the above claim(s) *3,7 and 9-11* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-2, 4-6,8, 12-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

In view of the Brief filed on 08 May 2006, PROSECUTION IS HEREBY REOPENED. A new ground of rejection is set forth below.

To avoid abandonment of the application, appellant must exercise one of the following two options:

(1) file a reply under 37 CFR 1.111 (if this office action is non-final) or a reply under 37 CFR 1.113 (if this Office action is final); or

(2) request reinstatement of the appeal.

If reinstatement of the appeal is requested, such request must be accompanied by a supplemental appeal brief, but no new amendments, affidavits (37 CFR 1.130, 1.131 or 1.132) or other evidence are permitted. See 37 CFR 1.193

Status of Application, Amendments, And/Or Claims

Claims 1-15 are pending. Claims 3, 7, and 9-11 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected Invention.

Claims 1-2, 4-6, 8, and 12-15 will be examined on the merit to the extent that they read on the elected species (i) –CO- $(CH_2)_X$-$(OCH_2CH_2)_m$OR, (ii) monomethoxy polyethylene glycol groups and (iii) a N-terminal residue.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claim 1-2, 4-6, 8, and 12-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Date et al (Oncogene, 17:3045-3054, 1998) in view of Bartley (US Patent No. 5,766,581).

The claims are drawn to a conjugate consisting of a NK4 molecule and a PEG having (i) a molecular weight of about 20-40 KDa, (ii) wherein –CO group of said PEG forms an amide bond with one of the amino groups of the N-terminal fragment of said NK4, (iii) wherein said PEG is selected from monoethoxy polyethylene groups, (iv) a

pharmaceutical composition comprising said conjugate and at least on pharmaceutically acceptable carrier, and (v) a composition comprising mono-pegylated NK4 conjugates wherein the PEG groups are attached to groups selected from the lysine side chains or to the N-terminal amino groups of NK4 molecules.

Date et al teach that NK4 is a 59 kDa protein which comprises four-kringle domains and functions as an antagonist of hepatocyte growth factor (HGF) in mitogenic, morphogenic and tumor inhibitory activities (page 3046, 2nd paragraph of the left column). Date et al do not teach attaching a polyethylene glycol (PEG) group having a molecular weight of about 20-40 KDa that forms an amide bond with the -NH2 groups of N-terminus amino acid or with a lysine residue of a NK4 polypeptide.

Bartley et al teach that the pegylation of a protein protects the protein from proteolysis and many proteins such as interferon, hemoglobin, superoxide dismutatse are in clinical trials for treating diseases. They teach a method of modifying proteins by attaching a branched or unbranched polyethylene glycol (PEG), and a pharmaceutical composition comprising the PEG modified protein that is pharmaceutically acceptable (col. 21 lines 31-34, line 49, col. 26, lines 29-37). They teach that the polymer can be selected from many groups including monoethoxy polyethylene glycol (col 21, lines 34-36). Further they teach mono-pegylation of megakaryocyte growth and differentiation factor (MDGF) in the molecular range of 12-25 kDa (see Example 12, Col. 41-44) and further suggest that a polymer of any molecular weight can be attached with a protein of interest (col. 21, line 47). The skill of attaching a PEG group to the amino group of a protein is high and one of skill in the art knows the chemistry of joining an acidic or

aldehyde group (-COOH, -CHO) with a –NH2 of the N-terminus amino acid or lysine residue of a protein that forms an amide bond. Bartley et al teach that a peg group can be attached the N-terminus –NH2 group of the lysine residue or to the N-terminus amino acid of the protein though an amide bond between a mono methoxy-PEG and the NH2 group of the protein (col. 20, lines 53-59, col. 21, lines 11-13).

It would have been prima facie obvious to the person of ordinary skill in the art at the time the invention was made to attach mono methoxy PEGs in the range of molecular weight 12-25 kDa or any molecular weight as suggested by Bartley to the N-terminus amino acid or to a lysine amino acid of NK4 of Date et al through an amide bond in order to increase protein stability, improve in vivo pharmacokinetics, and to prepare a pharmaceutical composition comprising the PEGylated protein. The person of ordinary skill in the art would have been motivated to attach a PEG groups of about 12-25 kDa or any other molecular weight (including in the range of 5-40) to a NH2 of N-terminus amino acid or a lysine of NK4 or with a reasonable level of success because Date et al show that NK4 molecule has antagonistic activities of HGF and pegylated molecules have a prolonged half-life and are already successful in clinical trials as taught by Bartley.

Claims 14 and 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Date et al and Bartley et al as applied to claims 1-2, 4-6, 8, and 12-13 above, and further in view of and further in view of Veronese et.al. (US Patent 6,528,485 B1).

The claimed invention is further drawn to a pharmaceutical composition comprising conjugates of NK4 monopegylated with PEG that have molecular weight of

20-40 kDa where conjugate comprises at least 90% or 92% pegylated NK4 and unpegylated NK4 molecules in the composition.

The teachings of Date in combination of Bartley et al are summarized as set forth supra. Date in combination of Bartley do not teach a pharmaceutical of a monoPEGylated conjugate comprising at least 90% or 92% of the total NK4 molecules. Veronese et.al. teach making PEGylated proteins and purifying them to greater than 92% purity. Veronese et al teach that the high purity a PEGylated proteins result in a better bioavailability and pharmacokinetics profile in vivo.

It would have been prima facie obvious to the person of ordinary skill in the art at the time the invention was made to prepare a pharmaceutical composition comprising conjugates of NK4 monopegylated as taught by Date in combination of Bartley and further purify the conjuage to comprise at least 90% or 92% monopegylated NK4 of the total pegylated and unpegylated protein as taught by Veronese et al. The person of ordinary skill in the art would have been motivated to prepare a pharmaceutical composition comprising a monoPEGylated conjugate with at least 90% or 92% of the total NK4 molecules with reasonable level of success as Veronese et al teach making a high purity a PEGylated protein that results in an improved bioavailability and pharmacokinetics in vivo.

Conclusion

No claim is allowed.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Chamow et al. (Bioconjugate Chem. 5: 133-140, 1994). They teach attaching monomethoxy-PEGs (branched or unbranched) to the N-terminus amino residue of CD4.

Gaertner et al. (previosly presented, Bioconjugate Chem. 1996). They teach that the PEG groups in the range of 5 to 40 kDa should be attached to a protein for an improved bioavailability (page 44, first sentence of the 2nd paragraph of conclusion).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gyan Chandra whose telephone number is (571) 272-2922. The examiner can normally be reached on 9:00-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol can be reached on (571) 272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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